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Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Docket No; 00D-0084
Draft Guidance for Industry on Special Protocol Assessment

Dear Sirs

This provides comments on the above-mentioned draft guidance document. Procter & Gamble Pharmaceuticals (P&GP) welcomes the development of a guidance to clarify the procedures to be adopted by CDER and CBER regarding evaluation of issues related to the adequacy of certain proposed studies. Specific comments are as follows;

II. Background
Section 119(a) of the Modernisation Act states that "the Secretary shall meet with a sponsor ... if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim". Hence, regardless of the wording in the PDUFA Reauthorisation Performance Goals and Procedures document, section 119(a) of the Act does not specify that such trials must be designated phase III trials. P&GP can envisage the primary basis of an efficacy claim coming from non-phase III trials, eg in the case of a product pursuing accelerated approval. P&GP therefore requests that references to 'phase III' protocols be deleted from this Guidance, eg see lines 24, 27, 56-57, 94, and 229, and replaced with the FDAMA language, "clinical trials intended to form the primary basis of an effectiveness claim".

III.A Timing of Request.
P&GP requests that the statement 'special protocol assessment will not be provided after a study has begun' be deleted (see line 70). P&GP can envisage circumstances where protocol assessment may be important after initiation of a carcinogenicity, stability or clinical study. This could be due to availability of new data and/or new global regulatory guidance after the study start, or there may be other instances where the outcome of the Special Protocol Assessment may not affect the conduct of an ongoing study, ie which of 2 endpoints already included in a protocol will be primary.

III.A.1 Carcinogenicity Protocols
P&GP notes that the draft Guidance specifies a total 75-day review timing for carcinogenicity protocols, when submission of a notice of intent and background package is required 30 days in advance of the official request for protocol assessment (lines 75-79). In order to comply with the PDUFA goals, P&GP requests that the requirement for this 30 day 'presubmission' be deleted.

III.A.2 Stability Protocols
P&GP considers that the current draft wording (lines 82-83) infers that an end-of-phase 2 or pre-phase 3 meeting is mandated. We therefore request that wording similar to that used under III.A.3 for clinical protocols be used, ie the Agency may provide a comprehensive protocol assessment without requiring an end-of-phase II / pre-phase III meeting if the Agency is already familiar with the developmental context of a proposed stability study.

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P&GP believes that it may not always be necessary for a product to be in phase III development prior to requesting Special Protocol Assessment for a stability study, eg in cases where the product has a very short phase III clinical programme. We therefore request that the sentence on lines 87-88 be amended; "~~The product should be in phase III development and product characterisation~~ Definition of the intended commercial product should be complete."

III.D Content of a Request
P&GP requests the following clarification to lines 144-146; "The sponsor should clearly describe to the best of their ability, with detail appropriate to the phase of development, any regulatory outcomes ..." This recognises that it may not always be possible at that particular stage of development to describe detailed specific claims, comparative claims, and/or labelling that would be supported by a particular study.

IV.B Assessment of the Protocol
Lines 171-172. To make the guidance less prescriptive, P&GP requests that this sentence be changed as follows; "... will answer any questions that are appropriate, including for example, providing comments ...".

Lines 175-176, P&GP requests that this sentence be changed as follows; "Any significant change in the underlying data, assumptions, and information could affect the assessment of the protocol." This recognises that changes may occur during the conduct of the resulting agreed-to protocol which would not necessarily impact the Agency's assessment of the adequacy of the trial. P&GP looks for assurance that the Agency will not point to non-significant changes as a rationale for why Special Protocol Assessments are invalidated.

IV.B.2 Advisory Committee Review
P&GP acknowledges release of the December 1999 Draft Guidance, 'Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drugs and Convened by the Centre for Drug Evaluation and Research, Beginning on January 1, 2000.' P&GP considers that information shared with Advisory Committees as part of the special protocol assessment process should be exempt from public disclosure, and that discussion of special protocol assessment requests by an Advisory Committee should take place during a closed portion of the meeting. P&GP therefore requests that the guidance clarifies the Agency's position with respect to the public nature of Advisory Committee meetings dealing with special protocol assessment requests.

There could likely be substantial delays to research associated with the necessity for an advisory committee review. Therefore, P&GP proposes that it may be more prudent to seek advice solely (as described in lines 190-191) from selected advisory committee members, outside consultants, or special Government employees.

VI.B Changes in Documented Special Protocol Assessments
Lines 231-232, P&GP requests change; ".. the Agency will not later alter its perspective on the issues of design, execution, or analyses unless substantial public health concerns ...".

Line 236, P&GP requests change; "Failure of a sponsor to follow those specific elements of a protocol that ~~was~~ were agreed upon with the Agency .."

Line 239, P&GP requests change; "If the relevant data, assumptions or information provided by the sponsor in a request for specific protocol assessments change significantly .."

P&GP requests that the Guidance clarifies that the onus is on FDA to notify the sponsor if any data routinely submitted during the development programme (eg in IND amendments or annual reports) is considered by FDA to alter their agreements to specific elements of a protocol that were agreed upon with the Agency.

VI.C Personnel changes.
P&GP disagrees that changes in personnel within the sponsor company should not impact documented special protocol assessment. P&GP considers that the sponsor should be free at any time to propose changes to a prior agreement, and to submit a proposed new protocol for special assessment. P&GP therefore request that lines 254-255 are changed to; "Personal preferences of new individuals ~~on either team should~~ at FDA shall not alter any documented special protocol assessment." This reflects the fact that FDA personnel should not propose changes to a prior agreement in the absence of substantial public health concerns, or significant relevant new data (see comments related to section VI.B).

VII Dispute Resolution
P&GP considers that delaying initiation of a trial until resolution of dispute with FDA regarding the study design may not be appropriate in all circumstances. P&GP considers that a study may be initiated with opportunity for initiation and/or resolution of special protocol assessment after the study is underway, such as instances where there will be no impact on what information is being collected, eg which of 2 endpoints already being collected will be primary. P&GP therefore requests that the sentence on lines 258-259 be deleted ("Any dispute regarding study design should be resolved prior to initiation of the trial").

If you should have any questions regarding these comments, please do not hesitate to contact me.

Yours faithfully

SMDenegri

Susan M Denegri
Section Head, US Regulatory Affairs

cc Alan Goldhammer, PhRMA

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